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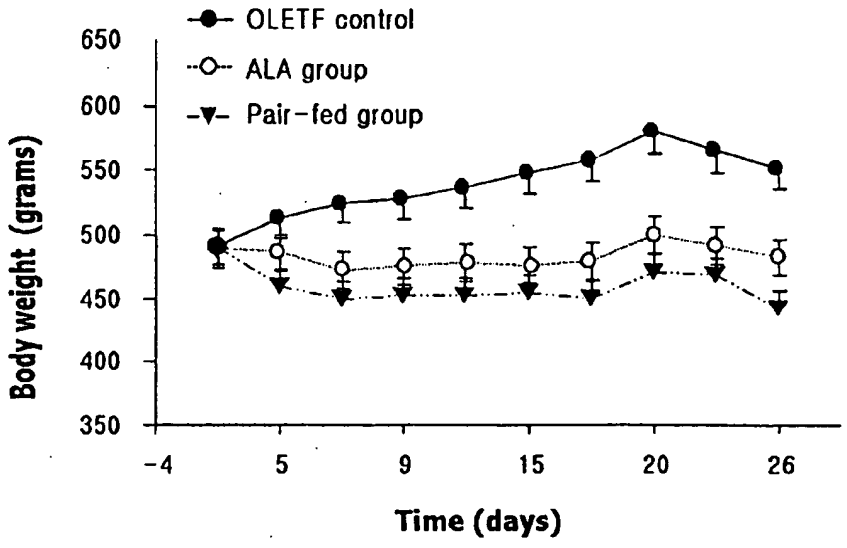
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: MEDICINE FOR TREATING OBESITY



(57) Abstract: The present invention relates to a new medicine for treating obesity, and more particularly to a medicine for treating obesity comprising α-lipoic acid. Moreover the present invention provides compositions for treating obesity or decreasing appetite comprising α-lipoic acid, pharmaceutically acceptable carriers and additives.

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MEDICINE FOR TREATING OBESITY

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to novel anti-obesity agent, and more particularly, to the use of α-lipoic acid as anti-obesity agent.

2. Description of the Prior Art

Obesity is one of the most common medical disorders, which affects 30-40% of the population of which 10% may be severe and morbid. Complications of obesity include insulin resistance, diabetes mellitus, hypertension, cardiovascular disease, pseudotumor cerebri, hyperlipidemia, sleep apnea, cancer, pulmonary hypertension, cholecystitis, and osteoarthritis. As a result, keen attention is being paid to anti-obesity agent.

Unfortunately, current treatments of obesity are largely unsuccessful with a high failure rate. Although obese patients try to reduce weight by diet and exercise, this failure may be due to the fact that the condition is strongly associated with genetically inherited factors that contribute to increased appetite, preference for highly caloric foods, increased lipid synthesis metabolism. Therefore, a new pharmacological agent to successfully reduce weight is needed.

A compound known as α-lipoic acid ($C_8H_{14}O_2S_2$) was first isolated by Reed and coworkers and they named the compound α-lipoic acid after isolating trace element in liver, the structure of compound was elucidated by synthesis. α-lipoic acid was known as a new vitamin by the fact that unknown trace element in liver or yeast extract is a lactic acid bacteria growth factor. α-lipoic acid is known by a variety of names, including

thioctic acid; 1,2-diethylene-3 pentanoic acid; and 6,8-thioctic acid. It functions as a thiamine related cofactor in the oxidative decarboxylation system of α-keto acids such as pyruvate, α-keto glutarate. Although admitted that α-lipoic acid is an essential material in metabolism, it is not clear that α-lipoic acid is necessary for food intake in higher animals. The experiment of lipoic acid deficiency for animals is still unsuccessful.

More recently, a great deal of attention has been given to possible antioxidant functions for α-lipoic acid, and its reduced form, dihydrolipoic acid (DHLA). It is reported that α-lipoic acid, or its reduced form, DHLA, reacts with reactive oxygen species such as superoxide radicals, hydroxyl radicals, peroxyl radicals, and singlet oxygen and it also protects cell membrane by reacting with vitamin C and glutathione. α-lipoic acid administration has been shown to be beneficial in a number of oxidative stress besides.

However, it is not known α-lipoic acid use as anti-obesity agent.

SUMMARY OF THE INVENTION

Accordingly, the present invention has an object to provide α-lipoic acid as anti-obesity agent.

There is provided a composition for treating obesity comprising α-lipoic acid, and a pharmaceutically acceptable carrier and additive.

In order to achieve the object of the present invention, a anti-obesity agent comprising α-lipoic acid.

Commercial α-lipoic acid may be used as anti-obesity agent of the present invention.

The anti-obesity agent in the present invention may be used with α-lipoic acid alone or mixed with other treatments of obesity. If necessary, the anti-obesity agent in

the present invention may be mixed with various pharmaceutically acceptable additives such as excipients, disintergrants, freshners and lubricants.

The anti-obesity agent in the present invention may be oral or parenteral agents, but oral agents are desirable.

When α-lipoic acid of the present invention is injected into OLETF white rats as animal models having obese diabetes, the OLETF rats are shown to reduce the amount of insulin and lose weight. Additionally, the mRNA expression of uncoupling protein1 UCP1 which emits energy as heat in brown and white adipose issues of the rats injected with α-lipoic acid significantly increases. It is shown from the above results that the effect of α-lipoic acid on obesity improvement results from induction of decrease in ingestion and the increase in expression of UCP1 in brown and while adipose tissues.

BRIEF DESCRIPTION OF THE DRAWINGS

The present invention will be explained in terms of exemplary embodiments described in detail with reference to the accompanying drawings, which are given only by way of illustration and thus are not limitative of the present invention, wherein:

Fig. 1 is a graph illustrating the effect of anti-obesity agent of the present invention on weight loss;

Figs. 2a and 2b are a Northern blot and a graph illustrating the effect of anti-obesity agent of the present invention inhibiting UCP1 expression in brown adipose tissues; and

Figs. 3a and 3b are a Nothern blot and a graph illustrating the effect of anti-obesity agent of the present invention inhibiting UCP1 expression in white adipose tissues.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Example 1: Weight change experiment

OLETF rats(21 weeks) were classified into control group (n=6), feeding group for α-lipoic acid(n=6) and pair-feeding group (n=6). The addition of at 0.6% α-lipoic acid to normal rat feed was administrated to the OLETF rats for 26 days in feeding group for α-lipoic acid(ALA group). Normal rat feed was administrated to the OLETF rats of the control group and pair-feeding group for the same period. The same amount of feed, which was administrated to the OLETF rats of feeding group for α-lipoic acid on the previous day, was administrated to the OLETF rats of pair-feeding group.

The weight change was observed by weighing the OLETF rats every three days after weighing the OLETF on the first day. Then, Table 1 and Fig. 1 shows the averaging results.

[Table 1]

	Weight on the first day(g)	Weight on the 26th day (g)	Intake of feed (g/day)
Control	490.7 ± 18.3	579.9 ± 25.8	36.1 ± 2.0
α-lipoic acid group	490.0 ± 7.9	471.2 ± 15.6*	27.2 ± 2.8
Pair-feed group	488.5 ± 11.0	496.2 ± 6.5**	27.2 ± 2.8

* $P < 0.05$

** $P < 0.05$

As shown in Table 1 and Fig. 1, the three experimental groups show little difference in weight on the first day. However, the amount of feed intake in the OLETF rats of α-lipoic acid group significantly decreases in comparison with the control group. The weight of the OLETF rats of α-lipoic acid group is shown to decrease on the 26th day than on the first day. The increase in body weight in α-lipoic acid is shown to be

significantly small than that of Pair-fed group. Accordingly, it is suggested that α-lipoic acid of the present invention is highly effective material for treating obesity than other treating methods reducing amount of meals.

Example 2: Measuring UCP1 mRNA in brown and white adipose tissues

After 26 days, OLETF rats in control group (n=6), α-lipoic acid group (n=6) and pair-feeding group (n=6) were sacrificed. Then, their brown and white adipose tissues were isolated. After each adipose tissue was homogenized, RNA was isolated by using TRIZOL solution (Life Technologies Co., Grand Island, NY, USA) with guanidium thiocyanate method using phenol/chloroform. From these RNAs, the degree of mRNA expression of UCP1 in brown and white adipose tissues was measured by Northern blot analysis, respectively and quantitative analysis was performed with densitometry. Then the result of brown adipose tissue is shown in Figs. 2a and 2b, and the result of white adipose tissue is shown in Figs. 3a and 3b.

As shown in Fig. 2a, the UCP1 mRNA expression, which emits energy as heat in brown adipose tissue, significantly increases in feeding group for α-lipoic acid in comparison with control group.

As shown in Figs. 3a and 3b, ALA group express UCP1 in white adipose tissue which cannot express UCP1 in normal condition.

As discussed earlier, α-lipoic acid as anti-obesity agent of the present invention is shown to have anti-obesity effect in OLETF white rats. The effect results from decrease in ingestion and increase in expression of UCP1 which emits energy as heat in brown and white adipose tissues. Accordingly, α-lipoic acid as anti-obesity agent of the present invention can be useful for excellent anti-obesity agent and appetite suppressant to various obese symptoms.

WHAT IS CLAIMED IS:

1. An anti-obesity agent comprising α-lipoic acid.

2. A composition for treating obesity comprising α-lipoic acid, and a pharmaceutically acceptable carrier and additive.

3. An appetite suppressant comprising α-lipoic acid.

4. A composition for suppressing appetite comprising α-lipoic acid, and a pharmaceutically acceptable carrier and additive.

Fig. 1

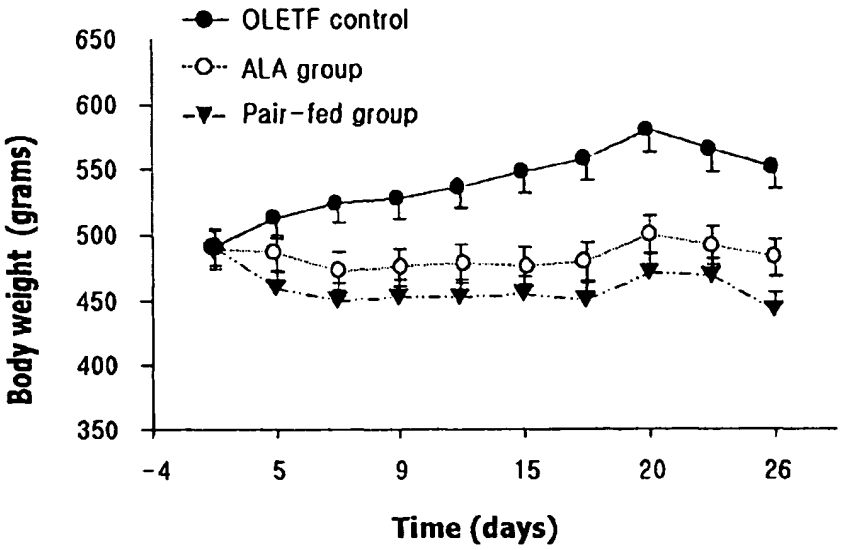

OLETF control
ALA group
Pair-fed group
650
600
550
500
450
400
350
Body weight (grams)
-4
5
9
15
20
26
Time (days)

Fig. 2a

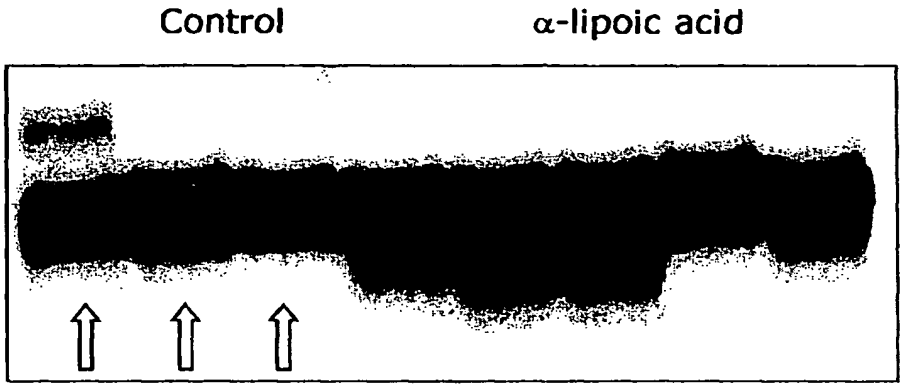

Control
α-lipoic acid

Fig. 2b

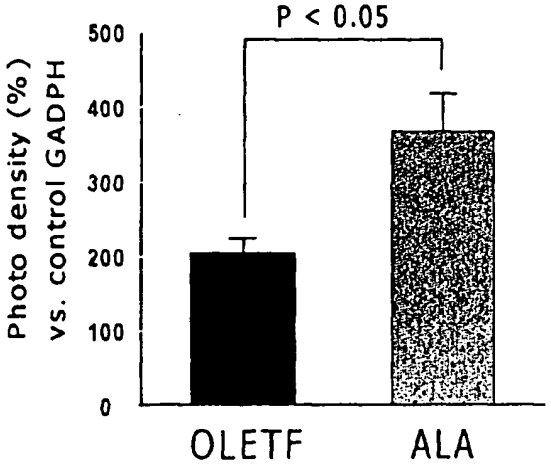
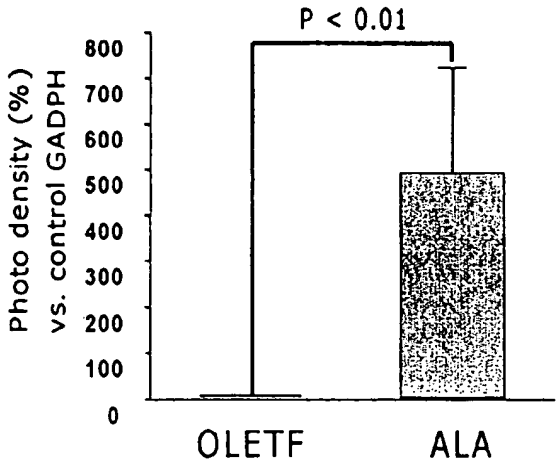

P < 0.05
Photo density (%)
vs. control GADPH
500
400
300
200
100
0
OLETF
ALA

Fig. 3a

CONTROL ALA

Fig. 3b



INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR02/01072

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 A61K 31/381

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN on line; KIPASS; ESPACENET

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/55331 A1 (Dean, J.), 4. Nov. 1999, abstract	1-4
A	EP 935962 A1 (Alken, R.G.), 18. Aug. 1999, see the whole document	1-4
A	WO 97/10808 A1 (Perricone, N.V), 27. Mar. 1997, see the whole document	1-4
A	US 5,962,030 A1 (Stuart A. F.), 5. Oct. 1999, see the whole document	1-4

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevence

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevence; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR02/01072

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 99/55331 A1	4. Nov. 1999	DE 19818563 A1	28. 10. 1999
EP 935962 A1	18. Aug. 1999	US 20020042444 A1	11. 04. 2002
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